REMARKS

Claims 1-30 are pending in this application. The Examiner previously withdrew claims 7-27 and 29-30 for being drawn to a non-elected invention. Applicants herein cancel claims 1 and 4, and amend claims 2-3 and 5-6. Upon entry of these amendments, claims 2-3 and 5-30 are pending with claims 2-3, 5-6 and 28 under active consideration. In addition, Applicants herein amend paragraphs [0010], [0011] and [0112] of the specification.

Applicants have amended claims 2 and 5 to incorporate the implicit requirement that inhibitors of phosphodiesterases decrease cAMP degradation, as defined at paragraph [0039] and discussed at paragraphs [0071] and [0076]. Applicants respectfully submit that such amendment does not limit the scope of claims 2 and 5 based on a proper determination of the claims as originally filed, as discussed below. Applicants have also amended claims 2 and 5 to rewrite the claims in independent form.

Applicants have amended claims 3 and 6 to recite that the phosphodiesterase inhibitor is an inhibitor of "PDE4," support for which may be found throughout the specification notably at paragraph [0076]. Applicants have also amended claims 3 and 6 to place the claims in proper dependent form by changing "A method" to "The method."

Applicants have amended claim 28 to delete the recitation of "Ariflo® (SmithKline Beecham)." Applicants respectfully submit that such amendment does not limit the scope of claim 28 because "Ariflo" is a trademark for the compound c-4-cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl)-r-1-cyclohexanecarboxylic acid, which is also present in claim 28.

Applicants have amended the specification at paragraphs [0010], [0011] and [0112] to spell out in full the first instance of the following: "phosphodiesterase" (PDE), "human chorionic gonadotropin" (hCG) and "radioimmunoassay" (RIA).

In view that the amendments to the claims and the specification are supported by the application as originally filed, Applicants respectfully submit that no new matter has been added. Accordingly, Applicants respectfully request entry of these amendments and remarks into the file history of the present application.

1. Objections

At page 3 of the Office Action, the Examiner objected to the disclosure for informalities. The Examiner requested that "PDE", "hCG" and "RIA" be spelled out in full for the first instance

of use. Applicants respectfully traverse the objection. As requested by the Examiner, Applicants have amended the specification to spell out in full "phosphodiesterase," "human chorionic gonadotropin" and "radioimmunoassay" for the first instance of use. Accordingly, Applicants respectfully request withdrawal of the objection.

2. Patentability Arguments

a. 35 U.S.C. § 112, first paragraph

(1) The rejection of claims 2-3, 5-6 and 28 under 35 U.S.C. § 112, first paragraph, for lack of possession of the claimed invention

At page 4 of the Office Action, the Examiner rejected claims 1-6 and 28 under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the written description requirement. Applicants respectfully traverse the rejection. Applicants respectfully submit that the Examiner has mischaracterized the scope of the claimed invention by failing to take into account the entire specification.

As a first step in determining compliance with § 112, ¶ 1, examiners are instructed to determiner the scope of each claim. *See* Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111 (the "Written Description Guidelines"). Each claim is to be given its "broadest reasonable interpretation in light of and consistent with the written description." *See* Written Description Guidelines at page 1105 (emphasis added). Examiners are then to determine from the standpoint of one of skill in the art at the time the application was filed whether there is sufficient disclosure to show possession of the claimed invention as a whole. *See* Written Description Guidelines at page 1105.

(a) Scope of the Claims

- Claims 1 and 4

The Examiner mischaracterized the scope of previously pending independent claims 1 and 4. This mischaracterization was then subsequently applied to dependent claims 2-3, 5-6 and 28.

Claims 1 and 4 were directed to a method of inducing ovulation in a female by administering a "non-polypeptide cAMP level modulator". Paragraph [0039] of the specification provides a definition for "non-polypeptide cAMP level modulator" as follows:

> "Non-Polypeptide cAMP Level Modulator" refers to compounds that are not composed of amino acids in their entirety, irrespective

> of glycosylation, and act, directly or indirectly, to increase intracellular levels of cAMP.

(emphasis added). The definition is consistent with the use of for "non-polypeptide cAMP level modulator" throughout the specification, namely that ovulation may be induced by increasing cAMP levels.

In determining the scope of claims 1 and 4, the Examiner failed to take into account the cited definition for "non-polypeptide cAMP level modulator" as well as its use throughout the specification. Instead, the Examiner focused solely on the language of the claims themselves. At page 4 of the Office Action, the Examiner alleges that the scope of a modulator of cAMP levels includes inhibitors and stimulators of cAMP levels. Claims are to be given their broadest reasonable interpretation, but the Examiner has improperly enlarged the scope of the claims. Based on the recited definition of "non-polypeptide cAMP level modulator" and its use in the specification, the scope of the claims includes "stimulators" of cAMP levels, but not "inhibitors" of cAMP levels.

Claims 1 and 4 are cancelled by this amendment, but claims 2 and 5 have been rewritten in independent form thereby incorporating the limitations of claims 1 and 4. Applicants respectfully request reconsideration of the scope of claims 1 and 4, as it now applies to claims 2 and 5.

- Claims 2 and 5

The Examiner also mischaracterized the scope of claims 2 and 5, which are directed to a method of inducing ovulation in a female by administering a "phosphodiesterase inhibitor." Paragraph [0041] of the specification provides a definition for "phosphodiesterase inhibitor" as follows:

> "Phosphodiesterase Inhibitor" refers to chemical compounds which block or inhibit phosphodiesterases (PDE's) whose action is to inactivate their cyclic nucleotide targets (i.e., cAMP and cGMP) by hydrolytic cleavage of the 3'-phosphodiester bond, resulting in passive accumulation of specific cyclic nucleotides.

The definition provides that the scope of "phosphodiesterase inhibitor" includes all inhibitors of PDEs, regardless of the cyclic nucleic nucleotide target of the PDE. The definition is limited, however, by the requirement that the "phosphodiesterase inhibitor" is a species of "non-polypeptide cAMP level modulator." As discussed above, a "non-polypeptide cAMP level modulator" is used to increase cAMP levels. It is implicit, therefore, that the PDE target of the

PDE inhibitor degrades cAMP without regards to its ability to degrade other cyclic nucleotides (e.g., cGMP). Moreover, the PDE target may be specific or non-specific for cAMP, so long as it degrades cAMP.

In determining the scope of claims 2 and 5, the Examiner once again failed to consider the specification as a whole. In doing so, the Examiner rejected the claims because "the invention is unrelated to modification of cGMP level[s]." *See* Office Action at page 4. Applicants agree with the Examiner that the invention is unrelated to modification of cGMP levels. A proper determination of claim scope shows that the invention is related to increases in levels of cAMP, without regards to changes in cGMP levels. Accordingly, Applicants respectfully request reconsideration of the scope of the claims.

(b) Application of Written Description Guidelines

The Examiner rejected the claims for lack of written description based on an incorrect determination that claims 2-3, 5-6 and 28 encompassed inhibitors of all PDEs. The Written Description Guidelines require the examiner to evaluate only PDE targets that degrade cAMP. In addition, Applicants respectfully point out that the Examiner has mischaracterized Conti.

The disclosure of Conti includes the testing of inhibitors against PDE3, which degrades cAMP and cGMP. At pages 4-5 of the Office Action, the Examiner alleges that Conti shows that PDE3-specific inhibitors prevent oocyte maturation thereby inhibiting ovulation. This is a mischaracterization. Conti discloses that administration of a PDE3 inhibitor prevents meiotic maturation of oocytes in an *in vivo* model; however, ovulation is in fact induced. *See* column 18, lines 11-14. Applicants respectfully request that the Examiner provide a first determination of whether the claims satisfy the written description requirement.

b. 35 U.S.C. § 112, second paragraph

(1) The rejection of claims 1-6 and 28 under 35 U.S.C. § 112, second paragraph, as being indefinite

(a) claim 1

At page 6 of the Office Action, the Examiner rejected claim 1 under 35 U.S.C. § 112, second paragraph. The Examiner alleges that claim 1 is indefinite because the recitation "modulator" appears to refer to stimulators and inhibitors of cAMP levels for cAMP-specific and non-specific PDEs. Applicants respectfully traverse the rejection. Applicants respectfully submit that the Examiner has once again failed to consider the specification in its entirety.

It is a fundamental principal that applicants are their own lexicographers. The claims may define the invention the using any terms, so long as any special meaning is clearly set forth in the specification. *See* MPEP §§ 2173. As discussed above, the use of the term "modulator" refers to stimulators of cAMP levels without regards to cGMP. Accordingly, Applicants respectfully request that the rejection be withdrawn.

(b) claim 3

At page 6 of the Office Action, the Examiner rejected claim 3 under 35 U.S.C. § 112, second paragraph. The Examiner alleges that claim 3 is indefinite because the recitation "phosphodiesterase 4 isoform" appears to encompass subtypes of PDE4, but the specification does not define any subtypes thereof. Applicants respectfully traverse the rejection. Applicants amend claim 3 to change "inhibitor of a phosphodiesterase 4 isoform" to "inhibitor of PDE4." In view of "PDE4" having a clear meaning, Applicants respectfully request that the rejection be withdrawn.

(c) claim 28

At page 6 of the Office Action, the Examiner rejected claim 28 under 35 U.S.C. § 112, second paragraph. The Examiner alleges that claim 28 is indefinite for containing a trademark/trade name. Applicants respectfully traverse the rejection. Applicants herein amend claim 28 to delete the recitation of "Ariflo® (SmithKline Beecham)." Accordingly, Applicants respectfully request that the rejection be withdrawn.

c. 35 U.S.C. § 103

(1) The rejection of claims 1-3 and 28 under 35 U.S.C. § 103 for obviousness

At page 7 of the Office Action, the Examiner rejects claims 1-3 and 28 as allegedly being obvious over U.S. Patent No. 6,423,710 ("Martins") in view of U.S. Patent No. 5,958,926 ("Garvey"). Applicants respectfully traverse the rejection. Applicants respectfully submit that claims 1-3 and 28 are nonobvious over the cited references because the Examiner has failed to show that there is a reasonable expectation of success.

To establish a prima facie case of obviousness, there must be a reasonable expectation of success based on the combination of cited references. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Whether the combination of cited references has a reasonable expectation of success is determined at the time the invention was made. *See* Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

At the time the instant application was filed, there was tremendous uncertainty as to the *in vivo* role of cAMP in maturation and ovulation. Prior to the disclosure of the present application, most studies of maturation and ovulation were limited to *in vitro* systems: either isolated oocytes or cultured follicles. More importantly, cAMP levels had contrasting effects in the different *in vitro* systems. For example, the PDE inhibitor IBMX was tested to increase intra-oocyte cAMP levels in both *in vitro* systems. IBMX was shown to inhibit maturation of isolated oocytes, but induced maturation in cultured follicles. *See* Conti at column 4, line 63 to column 5, line 4. These conflicting *in vitro* results made it impossible to predict the effect of cAMP levels *in vivo*, although Conti hypothesized the following:

> [T]hese apparently contradictory observations may be due to opposing fluctuations of cAMP levels in the somatic granulosa and germ cells caused by selective expression and regulation of distinct PDE isoforms in the somatic and germ cell compartments of the follicle.

See column 5, lines 5-10 (emphasis added). A similar proposal to explain the conflicting *in vitro* effects of cAMP levels was disclosed by Tsafrifri et al., Dev Biol. 178:393-402 (1996)("Tsafrifri"), which is submitted on the Supplemental Information Disclosure Statement submitted herewith. Tsafriri discloses that selective suppression of granulosa cell cAMP-PDE may enhance gonadotropin induction of ovulation and oocyte maturation. *See* abstract. Notably, neither Conti or Tsafrifri actually test the *in vivo* role of cAMP levels in ovulation.

At pages 7-8 of the Office Action, the Examiner relies on Martins for the proposition that PDE4 inhibitors can in fact be used to induce ovulation by elevating cAMP levels within granulosa cells. Applicants note that the citation from Martins relied on by the Examiner cites Tsafrifri. *See* Martins, column 21, lines 3-6. As discussed above, Tsafrifri merely proposes an untested hypothetical model in an attempt to explain the conflicting *in vitro* effects of cAMP levels. Martins mischaracterizes the disclosure of Tsafrifri by stating that PDE4 inhibitors can in fact induce ovulation *in vivo*.

The hypothetical and untested *in vivo* model proposed by Conti and Tsafrifri requires selective suppression of PDEs in different cells and tissue types. Whether *in vivo* administration of PDE inhibitors would in fact induce ovulation based on increasing cAMP levels in such a complicated manner was completely unknown at the time the application was filed. Based on the contrasting *in vitro* results on cAMP levels in ovulation and the lack of *in vivo* experimentation, the cited references do not disclose with any certainty that increased cAMP

levels induce ovulation *in vivo*. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Martins, Conti and Tsafrifri disclose nothing more than an "invitation to try" inducing ovulation by administering a PDE inhibitor in order to increase cAMP levels. It is clear, therefore, that the Examiner has failed to provide a reasonable expectation of success. Accordingly, Applicants respectfully request that the rejection be withdrawn.

(2) The rejection of claims 4-6 under 35 U.S.C. § 103 for obviousness

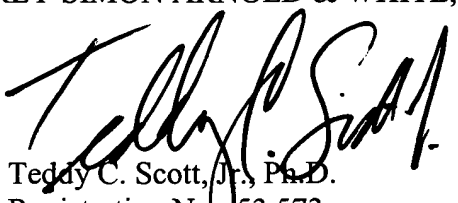
At page 8 of the Office Action, the Examiner rejects claims 4-6 as allegedly being obvious over U.S. Patent No. 6,423,710 ("Martins") taken with U.S. Patent No. 4,338,305 ("Corbin"), U.S. Patent No. 5,643,877 ("Zohar") and Bowman et al. ("Bowman"), and further in view of Travadi et al. ("Travadi"). Applicants respectfully traverse the rejection. The disclosures of Corbin, Zohar, Bowman and Travadi do not correct the above-discussed deficiency of the Examiner to provide a reasonable expectation of success. Accordingly, Applicants respectfully request withdrawal of the rejection.

3. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY SIMON ARNOLD & WHITE, LLP

Dated: October 18, 2004 By: 

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